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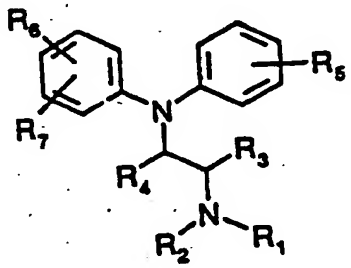
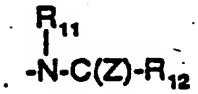
(54) Title: DIARYLDIAMINE DERIVATIVES AND THEIR USE AS DELTA OPIOID (ANT)-AGONISTS

(57) Abstract

A class of diaryldiamine derivatives of formula (I) in which R_1 and R_2, are each hydrogen, alkyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by an oxygen; R_3 and R_4, are each hydrogen, alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group; R_5 is hydrogen, hydroxy, alkoxy, thiol or alkylthio; R_6 is phenyl, halogen, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur; R_8 is alkyl, alkoxy or NR_9R_{10}, wherein R_9 and R_{10} are hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, aralkyl, or R_6 is a para or meta (a) group in which R_{11} and R_{12} are hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and, R_7 is hydrogen, alkyl, or halogen are potent and selective delta opioid agonists and antagonists, and are of use as analgesics and for treating pathological conditions which, customarily, can be treated with agonists and antagonists of the delta opioid receptor.



(I)



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DIARYLDIAMINE DERIVATIVES AND THEIR USE AS DELTA OPIOID (ANT)-AGONISTS

This invention is concerned with novel diaryldiamine derivatives, processes for their preparation, and their use in medicine.

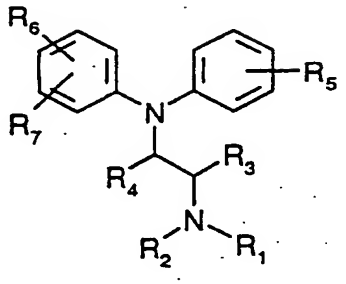
The presence of at least three populations of opioid receptors (*mu*, *delta* and *kappa*) is now well established and documented and all three appear to be present in the central and peripheral nervous system of many species including man (Lord J.A.H. et al., Nature 1977, 267, 495).

Activation of all three opioid receptor subtypes can lead to antinociception in animal models. In particular, studies with peptidic *delta* agonists have indicated that activation of the *delta* receptor produces antinociception in rodents, primates and can induce clinical analgesia in man (D. E. Moulin *et al.* Pain, 1985, 23, 213). Evidences exist that suggest a lesser propensity of *delta* agonists to cause the usual side-effects associated with *mu* and *kappa* activation (Galligan et al, J. Pharm. Exp. Ther., 1984, 229, 641).

Substituted diaryldiamines as intermediates for the synthesis of dibenzodiazepines, useful as antihistaminic and antianaphylaptic agents, have been previously described [Brit. Pat. 907646, Dr. A. Wonder A.G.; Hunziker *et al.*, Helv. Chim. Acta, 46, 2337, (1963)].
European Patent 508,334 (Green Cross Corp.) discloses oxygen-substituted diaryldiamines which are said to be inhibitors of TPA-induced mouse ear edema.
WO 93/15062 (The Wellcome Foundation Limited) discloses diphenylpiperazine derivatives which are said to be agonists at all three opiate receptors.

We have now discovered a novel class of diaryldiamine derivatives which are potent and selective *delta* opioid agonists and antagonists which may therefore be of potential therapeutic utility as analgesics, immunosuppressants to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agents, brain cell protectant, agents for treating drug and alcohol abuse, gastritis, diarrhoea, cardiovascular and respiratory diseases, cough, mental illness, epilepsy and, more in general, agents for those pathological conditions which, customarily, can be treated with agonists and antagonists of the *delta* opioid receptor.

According to the present invention, there is provided a compound, or a solvate or salt thereof of formula (I):



(I)

in which,

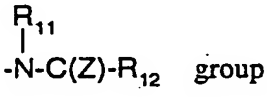
R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by an oxygen .

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl preferably methyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, preferably methoxy, thiol, alkylthio, preferably methylthio;

R_6 is phenyl, halogen, preferably bromine, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur,

R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl,

or R_6 is a para or meta  group

in which R_{11} and R_{12} which may be the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl, halogen, preferably chlorine.

Examples of R_1 and R_2 are methyl, ethyl, cyclopropylmethyl, allyl or together with the N, pyrrolidino.

Examples of R_3 and R_4 are hydrogen, methyl, ethyl, i-propyl, =O.

Examples of R_5 are hydrogen, hydroxy, methoxy.
Examples of R_6 are COMe, CO-i-Pr, COOEt, $CONH_2$, CONH-n-Pr, CON(Me)Et, CON(Me)i-Pr, $CONEt_2$, $CON(i\text{-}Pr)_2$, CONEt(i-Pr), $CON(\text{-}CH_2\text{-})_4$, NHCOi-Pr, NH_2, bromine, phenyl.

Examples of R_7 are hydrogen and methyl.

A first group of preferred compound of formula (I) are those in which each of R3 and R4 is hydrogen or C1-6 alkyl, preferably methyl or ethyl, and R_1, R_2, R_5, R_6 and R_7 are as defined above.

A second preferred group of compounds of formula (I) are those in which R_5 is an hydroxy or C1-6 alkoxy group, R_1, R_2, R_6 and R_7 are as defined above for formula (I) and each of R_3 and R_4 is hydrogen or C1-6 alkyl.

A particularly preferred group of compounds of formula (I) are those in which R_6 is a group -C(Z)-R_8 where R_8 is $C_{1\text{-}6}$ alkyl, $OC_{1\text{-}4}$ alkyl or NR_9R_{10} where R_9 and R_{10} are as defined above for formula (I), Z is oxygen, R_1, R_2 and R_7 are as defined above for formula (I), each of R_3 and R_4 is hydrogen or C1-6 alkyl, and R_5 is hydroxy or C1-6 alkoxy.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

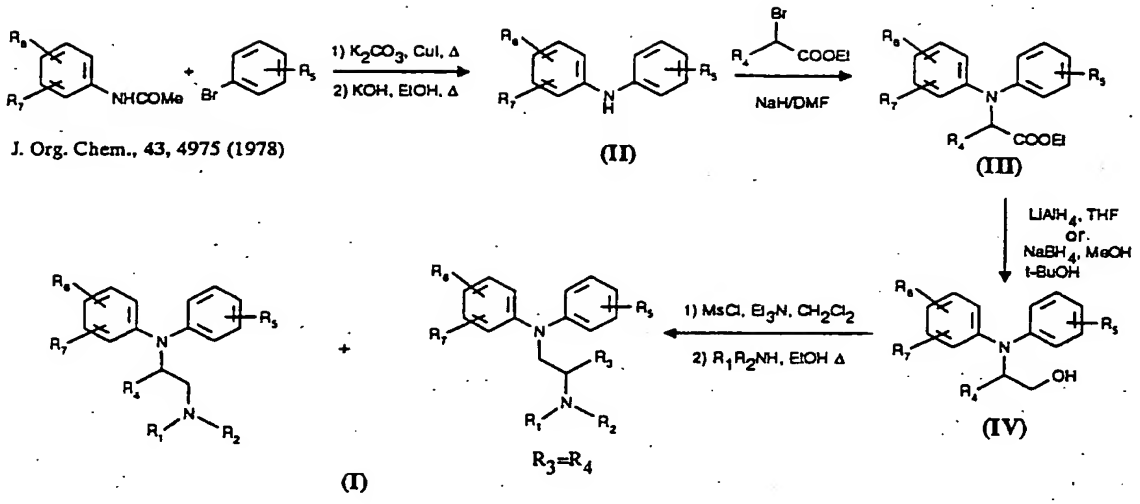
Examples of pharmaceutically acceptable salts of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

The compounds of formula (I) may exist in more than one stereoisomeric form, and the invention extends to all such forms as well as to their mixtures thereof, including racemates.

The present invention also provide a process for the preparation of a compound of formula (I). In general, these compounds may be prepared by the method illustrated in the following general reaction schemes, or by modification thereof, using readily available starting materials, reagents and conventional synthetic procedures. If a particular enantiomer of a compound of the present invention is desired, it may be synthesised starting from the desired enantiomer of the starting material and performing reactions not involving racemization processes or it may be prepared by chiral synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, compounds of formula (I) can be separated into their enantiomers by forming diastereomeric salts with an appropriate optically active acid, followed by fractional crystallization resolution and subsequent recovery of the pure enantiomers.

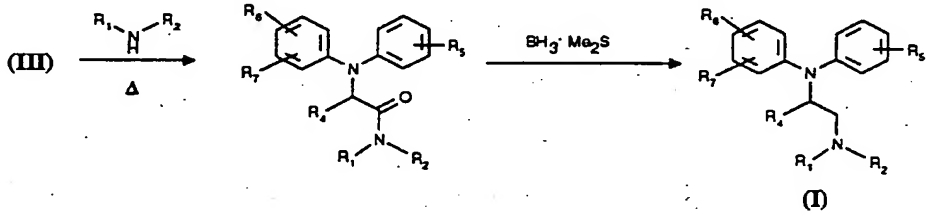
Compounds of general formula (I) may be obtained following the procedure described in Scheme 1. Compounds of general formula (II) may be synthesised starting from substituted acetanilides and substituted bromobenzene derivatives in presence of CuI and K_2CO_3 as described in *J. Org. Chem.*, 43, 4975 (1978). The bis-anilinic derivatives (II) may be alkylated using substituted α-bromo esters in presence of the NaH using DMF as solvent to obtain compounds of general formula (III). The ester group of these compounds may be reduced using $LiAlH_4$ in THF as solvent or, alternatively for compounds in which R_6 is a carbonyl containing group, using $NaBH_4$ in t-BuOH/MeOH as solvent to obtain compounds of general formula (IV). The alcohol derivatives are converted in their corresponding methanesulphonates and then treated with the appropriate amines obtaining compounds of general formula (I) along with their regioisomers in which $R_3 = R_4$.

Scheme 1



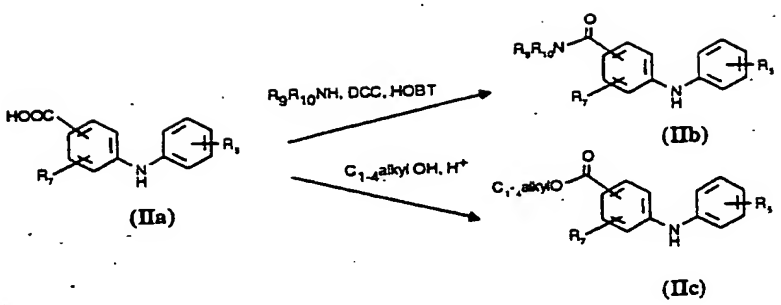
Alternatively, compounds of general formula (I) may be synthesised following the procedure described in Scheme 2. Esters of general formula (III), obtained as described in Scheme 1, may be treated with substituted amines under pressure. The corresponding amides may be reduced using $BH_3 \cdot Me_2S$ to obtain compounds of general formula (I) in which R_3 is H.

Scheme 2



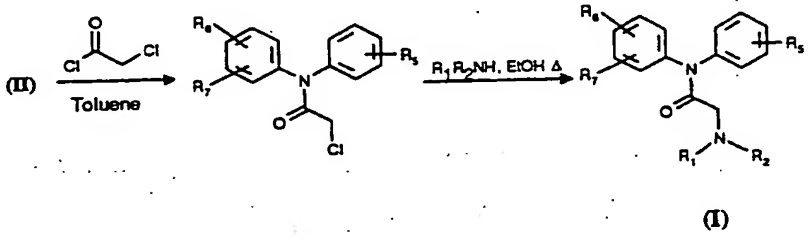
Compounds of general formula (I), in which R_6 is a group COR_8, where R_8 is as defined above, may be obtained starting from compounds of general formula (IIb) and (IIc), in turn obtained from compounds of formula (IIa) as outlined in Scheme 3. Amides (IIb) may be obtained treating the corresponding carboxylic acids (IIa) with the appropiates amines, using as condensing agents DCC/HOBT. Esters (IIc) are synthesised treating the compounds (IIa) with the corresponding alcohol in acidic media.

Scheme 3



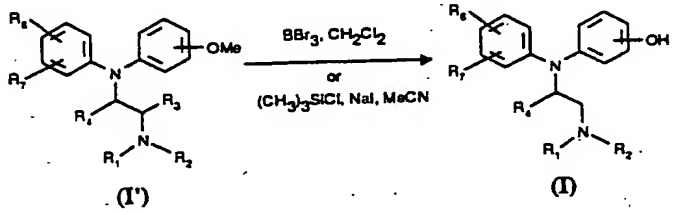
Compounds of general formula (I) where R_4 is =O may be prepared as described in Scheme 4. Compounds of general formula (II) are treated with chloroacetylchloride in boiling toluene. The resulting chloro derivatives are treated with the appropiate amines to obtain the final compounds of general formula (I).

Scheme 4



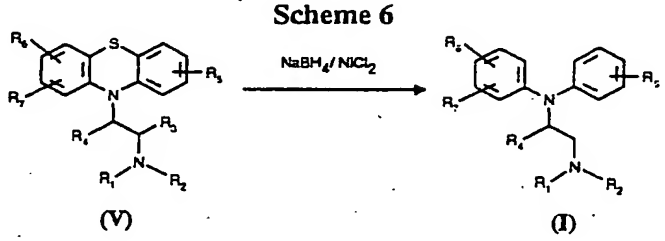
Compounds of general formula (I') in which R_5 is a MeO group, may be demethylated, for example, using BBr_3 in CH_2Cl_2 as solvent or alternatively, using $(CH_3)_3SiCl/NaI$ in boiling CH_3CN, to obtain other compounds of general formula (I) in which R_5 is OH. See Scheme 5.

Scheme 5



Compounds of general formula (I) may be obtained from phenotiazines of general formula (V) (described in EP0346238A1) removing the sulphur atom using $NiCl_2/NaBH_4$. See Scheme 6.

Scheme 6



(V) (I)

The compounds of formula (I) may be converted into their pharmaceutically acceptable salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example, hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

In general compounds of formula (I) acting as selective *delta* receptor ligands may be useful as analgesics, immunosuppressants to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agents, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough, mental illness, epileptic seizures and other neurologic disorders (herein after referred to as 'Conditions'). In particular, the activity of the compounds of formula (I) as *delta* agonists in standard tests indicates that they are of potential therapeutic utility as analgesic agents for the amelioration or elimination of pain.

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Conditions.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When

the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation

of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The activity of the compounds of the present invention as selective *delta* ligands is determined in radioligand binding assays as described below.

Mouse brain membranes were prepared as described by Kosterlitz (*Br. J. Pharmacol.*, 1981, 73, 939.). The binding of the preferential *delta* ligand [^{3}H]-[D-Ala^2,D-Leu^5]-enkephalin (DADLE) was evaluated at its K_D concentration (1.3 nM) in presence of 40 nM of the unlabelled *mu* ligand [D-Ala^2, MePhe^4, Gly-ol^5]-enkephalin (DAMGO). The binding of the *mu* ligand [^{3}H]-DAMGO (*Eur. J. Pharmacol.*, 1989, 166, 213) and of the *kappa* ligand [^{3}H]-U69593 (*Excerpta Medica*, 1990, 211) were carried out at 0.5 nM. The non-specific binding was determined in presence of naloxone (10 μ M) for all tritiated ligands. Binding data were expressed as percentage of inhibition and fitted the following equation: $f(x) = 100 \cdot X/(IC_{50} + X)$ where X are cold drug

concentration values. The IC_{50} obtained were used to calculate the inhibitory constants (K_i) accordingly to the Cheng and Prusoff relation (*Biochem. Pharmacol.*, 1973, 22, 3099).

The *delta* agonist/antagonist activity of the compounds of the present invention is determined in the mouse vas deferens (MVD) bioassay as described below.

Vasa deferentia were obtained from CD-1 mice and were suspended in a Mg^{2+}-free Krebs buffer at 37 °C. The tissues were electrically stimulated with pulse trains having the following parameters: train duration 50 ms, stimulus duration 2 ms, frequency of stimuli 50 Hz, maximal voltage 60-70 V, train frequency 0.1 Hz. Concentration response curves for each compounds were constructed cumulatively. Linear regression analysis and IC_{50} concentrations were evaluated according to Tallarida and Murray (*Manual of Pharmacological Calculations*, Springer Verlag NY, 1981).

The most potent compounds of the present invention showed affinities for the *delta* receptor ranging from 0.5 to 200 nM with *delta* selectivity ranging from 10 to 1500 times in respect to the other opioid receptor types. These compounds displayed also potent *delta* agonist or antagonist properties in the MVD preparation. Selective *delta* agonists (antagonised by the selective *delta* antagonist naltrindole) displayed IC_{50}s ranging from 1 to 500 nM. For example, the compound of Example 5 showed a $K_i\delta$ = 3.9 nM and in the MVD bioassay an IC_{50} = 7 nM (30 nM of NTI caused a 10-fold shift of the dose-response curve); the compound of Example 9 showed a $K_i\delta$ = 3.9 nM, $K_i\mu/K_i\delta$ = 148 and $K_i\kappa/K_i\delta$ = 153.

Mouse abdominal constriction (MAC) (*Proc. Soc. Exp. Biol. Med.*, 1957, 95, 729), mouse tail-flick (MTF) (*J. Pharm. Exp. Ther.*, 1941, 72, 74) and mouse tail-flick warm water (MTF-WW) (*Life Sci.*, 1986, 39, 1795) tests were adopted to evaluate the antinociceptive activity of the compounds of the present invention.

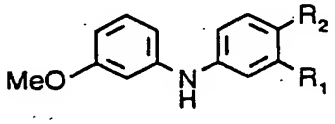
The following Preparations illustrate the preparation of intermediates, whereas the Procedures illustrate the preparation of compounds of the present invention. These compounds are summarised in the chemical table 4 and the analytical data are summarised in table 5.

PREPARATION 1

N,N-Diethyl-4-[N-(3-methoxyphenyl)amino]benzamide

3.7 g (2.3 mmol) of N-acetyl-*m*-anisidine, 10.6 g (41.4 mmol) of 4-bromo-N,N-diethylbenzamide and 0.42 g of CuI were heated to 100°C; 3 g (22.3 mmol) of K_2CO_3 were added and the resulting mixture was heated to 250°C for 2 hours. The residue was dissolved in CH_2Cl_2 and washed with H_2O, the organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was dissolved in 20 ml of absolute EtOH and refluxed for 2 h. The solvent was removed *in vacuo*, the residue was taken up in H_2O and the aqueous layer extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography (AcOEt/Hexane 6:4), yielding 3 g of the title compound.
IR cm^{-1} (neat): 3300, 1595, 1535.
MS (EI) m/z: 297.6 (M-1)

Compounds of general formula (II) described in Table 1 were obtained following the same procedure.



(II)

TABLE 1

NAME	R_1	R_2	IR cm^{-1} (neat)	MS (EI) m/z
4-Bromo-3'-methoxy diphenylamine	H	Br	3380, 1580, 1490	
3'-Methoxy-4-phenyl diphehylamine	H	Ph	3400, 1600, 1540	275.1
4-[N-(3-Methoxyphenyl)amino] benzoic acid	H	COOH'	3380, 1660, 1590	243.0
N,N-Diethyl-3-[N-(3-methoxyphenyl)amino] benzamide	$CONEt_2$	H	3280, 1600, 1580	298.0
3'-Methoxy-4-nitro diphenyldiamine	H	NO_2	3340, 1580, 1300	244.3

Compounds of general formula (II) may also be prepared according to the following procedure:

PREPARATION 2

1-[4-[[N-(3-Methoxyphenyl)]amino]benzoyl]pyrrolidine

2 g (8.2 mmol) of 4-[N-(3-methoxyphenyl)aminobenzoic acid, 2.2 g (16.4 mmol) of N-hydroxybenzotriazole and 1 ml (12.3 mmol) of pyrrolidine were dissolved in 40 ml of a 7:3 mixture of THF/CH_3CN, under a nitrogen atmosphere. The solution was cooled to 0°C and 3.4 g (16.4 mmol) of dicyclohexylcarbodiimide dissolved in 20 ml of CH_2Cl_2 were added. The reaction mixture was allowed to warm to room temperature during 1h., stirred an additional hour, then the precipitate was filtered off and the solvent was removed *in vacuo*. The residue was taken up with water and extracted with AcOEt, the organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting crude mixture was purified by flash chromatography (AcOEt), yielding 2.4 g of the title compound.

IR cm^{-1} (KBr): 3280, 1600, 1435;

MS (EI) m/z: 296.1.

N,N-diisopropyl-4-[N-(3-methoxyphenyl)amino]benzamide was obtained using the same procedure.

IR cm^{-1} (KBr): 3280, 1600, 1340;

MS (EI) m/z: 326.1.

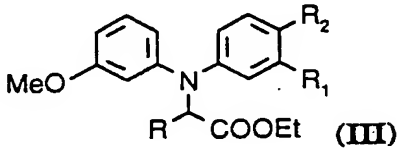
PREPARATION 3

(±)-N,N-Diethyl-4-[[N-(1-ethoxycarbonylethyl)-N-(3-methoxyphenyl)] amino]benzamide

2 g (51.6 mmol) of a 60% mineral oil suspension of NaH were placed, under a nitrogen atmosphere, in 100 ml of DMF. The resulting suspension was cooled to 0°C and 7.7 g (25.8 mmol) of N,N-diethyl-4-[N-(3-methoxyphenyl)amino] benzamide dissolved in 50 ml of DMF were added. After 1 h 8.4 ml (64.5 mmol) of ethyl 2-bromopropionate in 25 ml of DMF were added. The reaction mixture was allowed to warm to room temperature overnight, then H_2O was added, the organic layer was collected, dried over Na_2SO_4 and the solvent was removed *in*

vacuo. The crude reaction mixture was purified by flash chromatography (AcOEt/hexane 6:4), yielding 3.5 g of the title compound.
IR cm^{-1} (neat): 2980, 1740, 1610.
MS (EI) m/z: 398

Compounds of general formula (III) described in Table 2, were obtained following the same procedure.



(III)

TABLE 2

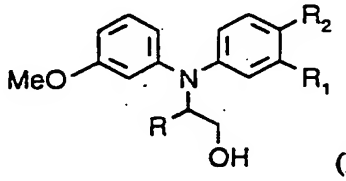
NAME	R	R_1	R_2	IR cm^{-1} (neat)	MS (EI) m/z
(±)-Ethyl-2-[N-(4-bromophenyl)-N-(3-methoxyphenyl)]amino propionate	Me	H	Br	2980, 1740, 1580	379 (M+1)
Ethyl-N-(4-bromophenyl)-N-(3-methoxyphenyl)]amino acetate	H	H	Br	1760, 1585, 1495	
(±)-Ethyl-2-[N-(4-biphenylyl)-N-(3-methoxyphenyl)]amino propionate	Me	H	Ph	1750, 1615, 1490	375.2
N,N-Diethyl-4-[[N-ethoxycarbonylmethyl-N-(3-methoxyphenyl)]amino] benzamide	H	H	$CONEt_2$	1750, 1620, 1595	384.1
(±)-N,N-Diethyl-4-[[N-(1-ethoxycarbonylpropyl)-N-(3-methoxyphenyl)]amino] benzamide	Et	H	$CONEt_2$	2980, 1740, 1620	412.2
(±)-1-[4-[[N-(1-Ethoxycarbonylethyll)-N-(3-methoxyphenyl)]amino]benzoyl] pyrrolidine	Me	H	$CON(CH_2)_4$	1755, 1615, 1590	396.0
(±)-N,N-Diisopropyl-4-[[N-(1-ethoxycarbonylethyl)-N-(3-methoxyphenyl)]amino] benzamide	Me	H	$CON(i\text{-}Pr)_2$	2980, 1740, 1620	426.2
(±)-N,N-diethyl-3-[[N-(1-ethoxycarbonylethyl)-N-(3-methoxyphenyl)]amino] benzamide	Me	$CONEt_2$	H	2980, 1740, 1635	398.1
(±)-Ethyl-2-[N-(4-nitrophenyl)-N-(3-methoxyphenyl)]amino propionate	Me	H	NO_2	2980, 1740, 1590	344.1

PREPARATION 4

(±)-N,N-Diethyl-4-[[N-(1-hydroxyprop-2-yl)-N-(3-methoxyphenyl)] amino]benzamide.

1.13 g (2.8 mmol) of (±)-N,N-diethyl-4-[[N-(1-ethoxycarbonylethyl)-N-(3-methoxyphenyl)]amino]benzamide were dissolved, under a nitrogen atmosphere, in 14 ml of *t*-BuOH and 0.27 g (7 mmol) of $NaBH_4$ were added. The reaction mixture was heated to reflux and 2.5 ml of MeOH were added during 1 h. The solution was refluxed 2h, then H_2O was added, the solvent was removed *in vacuo*, the residue was taken up in H_2O and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (AcOEt/hexane 9:1), yielding 0.5 g of the title compound.
IR cm^{-1} (neat): 3350, 2990, 1600;
MS (EI) m/z: 356.1.

Compounds of general formula (IV) and described in Table 3 were obtained following the same procedure.



(IV)

TABLE 3

NAME	R	R_1	R_2	IR	MS
(±)-2-[N-(4-Biphenylyl)-N-(3-methoxyphenyl)]aminopropanol	Me	H	p-Ph	3380, 2980, 1600	333.1
N,N-Diethyl-4-[[N-(2-hydroxyethyl)-N-(3-methoxyphenyl)]amino] benzamide.	H	H	p-$CONEt_2$	3400, 2980, 1600	342.1
(±)-N,N-Diethyl-4-[[N-(1-hydroxybut-2-yl)-N-(3-methoxyphenyl)]amino] benzamide.	Et	H	p-$CONEt_2$	3400, 1595, 1280	370.1
(±)-1-[4-[[N-(1-Hydroxyprop-2-yl)-N-(3-methoxyphenyl)]amino]benzoyl] pyrrolidine	Me	H	p-$CON(CH_2)_4$	3380, 1590, 1430	354.0
(±)-N,N-Diisopropyl-4-[[N-(1-hydroxyprop-2-yl)-N-(3-methoxyphenyl)]amino] benzamide.	Me	H	p-$CON(i\text{-}Pr)_2$	3360, 1600, 1265	384.2
(±)-N,N-Diethyl-3-[[N-(1-hydroxyprop-2-yl)-N-(3-methoxyphenyl)]amino] benzamide.	Me	p-$CONEt_2$	H	3400, 1600, 1490	356.2

PREPARATION 5

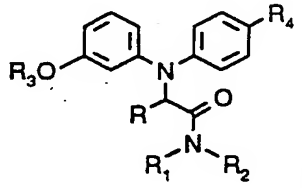
(±)-Ethyl-2-[N-(4-aminophenyl)-N-(3-methoxyphenyl)]amino propionate

1.5 g (4.3 mmol) of (±)-ethyl-2-[N-(4-nitrophenyl)-N-(3-methoxyphenyl)]amino propionate were dissolved in 50 ml of abs.EtOH; 150 mg of 10% Pd/C were added and the resulting mixture was hydrogenated in a Parr apparatus at 40 psi for 2 h. The catalyst was filtered off and the solvent removed *in vauo*, yielding 1.2 g of the tithe product.

IR cm^{-1} (neat): 3460, 3360, 1730;

MS (EI) m/z: 314.2.

Compounds of general formula (V) may be prepared according to the following procedure:



(V)

PREPARATION 6

(±)-1-[2-[[N-(4-Bromophenyl)-N-(3-methoxyphenyl)]amino]propionyl] pyrrolidine

6.2 g (16.4 mmol) of (±)-ethyl-2-[N-(4-bromophenyl)-N-(3-methoxyphenyl)] aminopropionate and 100 ml of pyrrolidine were placed in a medium-pressure apparatus and heated to 200°C overnight. The pyrrolidine was then removed *in vacuo*, the residue was taken up in CH_2Cl_2 and washed with 5% HCl. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*, yielding 6 g of the title compound.

IR cm^{-1} (neat): 2985, 1650, 1610;

MS (EI) m/z: 402 (M-1).

1-[2-[[N-(4-bromophenyl)-N-(3-hydroxyphenyl)]amino]acetyl]pyrrolidine was obtained following the same procedure.
IR cm^{-1} (KBr): 3180, 1630, 1590;
MS (EI) m/z: 374.1.

1-[2-[[N-(4-aminophenyl)-N-(3-methoxyphenyl)]amino]acetyl]pyrrolidine was obtained following the same procedure.
IR cm^{-1} (KBr): 3440, 3340, 1630;
MS (EI) m/z: 339.1.

PREPARATION 7

N,N-Diethyl-4-[[N-chloroacetyl-N-(3-methoxyphenyl)]amino] benzamide

3.7 g (12.4 mmol) of N,N-diethyl-4-[N-(3-methoxyphenyl)amino]benzamide and 1.2 ml (14.9 mmol) of chloroacetylchloride were heated to reflux in 40 ml of toluene for 2 h under a nitrogen atmosphere. The solvent was removed *in vacuo*, the residue taken up with H_2O and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (AcOEt/hexane 8:2), yielding 2.9 g of the title compound.
IR cm^{-1} (neat): 2980, 1695, 1635;
MS (EI) m/z: 374.

N,N-Diisopropyl-4-[[N-chloroacetyl-N-(3-methoxyphenyl)]amino] benzamide was obtained following the same procedure.
IR cm^{-1} (neat): 3280, 1690, 1620;

The compounds of the Examples described in Table 4, whose spectroscopic data are summarised in Table 5, were prepared by processes analogous to those described in Procedures A to I, which are fully described for some selected examples.

PROCEDURE A

(±)-N,N-Diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinyl-1-butyl)] amino]benzamide hydrochloride -Example 39- and **(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(1-pyrrolidinyl-2-butyl)]amino]benzamide hydrochloride** -Example 38-

To a solution of 1.0 g (2.7 mmol) of (±)-N,N-diethyl-4-[[N-(1-hydroxybut-2-yl)-N-(3-methoxyphenyl)]amino]benzamide in 10 ml of CH_2Cl_2 were added, under a nitrogen atmosphere and at 10°C, 0.6 ml (4.3 mmol) of Et_3N and 0.3 ml (4.3 mmol) of methanesulfonylchloride dissolved in 4 ml of CH_2Cl_2.After 90 min. the reaction mixture was poured in water, the layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was dissolved in 50 ml of toluene, 5 ml of pyrrolidine were added and the solution heated overnight at 90°C. The solvent was removed *in vacuo*, the residue brought to acidic pH with 5% HCl and the aqueous layer extracted with Et_2O, then brought to pH 14 with 15% NaOH and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash chromatography [(i-Pr)$_2$O/i-PrOH/conc. NH_4OH 98:2:0.5] yielding, after acidification with Et_2O/HCl, 200 mg of the product showing the higher Rf, corresponding to (±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(1-pyrrolidinyl-2-butyl)]amino]benzamide hydrochloride and 170 mg of the product showing the lower Rf, corresponding to (±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinyl-1-butyl)] amino]benzamide hydrochloride.

PROCEDURE B

(±)-N,N-Diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide -Example 31- and **(±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino] benzamide** -Example 30-

To a solution of 2.0 g (5.6 mmol) of (±)-N,N-diethyl-4-[[N-(1-hydroxyprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide in 20 ml of CH_2Cl_2 were added, under a nitrogen atmosphere and at 10°C, 1.25 ml (9.0 mmol) of Et_3N and 0.69 ml (9.0 mmol) of methanesulfonylchloride dissolved in 8 ml of CH_2Cl_2. After 90 min the reaction mixture was poured in water. The organic layer was washed with brine,

dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was dissolved in 30 ml of a 33% ethanolic solution of dimethylamine, the reaction mixture was placed in a medium-pressure apparatus and heated overnight at 80°C. The solvent was removed *in vacuo*, the residue brought to acidic pH with 5% HCl and the aqueous phase extracted with Et_2O, then brought to pH 14 with 15% NaOH and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 94.5:5:0.5), yielding 790 mg of the product showing the higher Rf, corresponding to (±)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide, and 645 mg of the product showing the lower Rf, corresponding to (±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide.

PROCEDURE C -Example 3-
(±)-N-(4-Bromophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoethanamine citrate

A solution of 2.6 g (6.4 mmol) of (±)-1-[2-[[N-(4-bromophenyl)-N-(3-methoxyphenyl)]amino]propionyl]pyrrolidine in 80 ml of dry THF was refluxed under a nitrogen atmosphere, then 4.2 ml (41.6 mmol) of a 10 M solution of $BH_3 \cdot Me_2S$ were added slowly. After 4 h. the solution was cooled to 0°C and 15 ml of H_2O, 15 ml of 10% HCl and 15 ml of 37% HCl were added respectively. the reaction mixture was brought to reflux for 4 h then cooled and the volatiles removed *in vacuo*. The residue was taken up in water, brought to pH 14 with 40% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 98:2:0.4), yielding 1.5 g of the title compound as a free base. 150 mg of product were dissolved in MeOH, an equimolar amount of anhydrous citric acid was added, the solvent was removed *in vacuo* and the resulting solid triturated with Et_2O, yielding 100 mg of the title compound.

PROCEDURE D -Example 2-
(±)-N-(4-Bromophenyl)-N-(3-hydroxyphenyl)-α-methyl-1-pyrrolidinoethanamine hydrochloride

0.85 ml (9 mmol) of boron tribromide were dissolved in 15 ml of dry $CHCl_3$ under a nitrogen atmosphere. 1.6 g (1.5 mmol) of (±)-N-(4-bromophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoethanamine dissolved in 7 ml of dry $CHCl_3$ were added at room temperature. After 2 h. the solution was poured onto 15 g of crushed ice containing 1.5 ml of concd. NH_4OH and stirred for 20 min. The layers were separated and the organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 94.5:5:0.5). The resulting solid was dissolved in MeOH, the solution was brought to acidic pH with Et_2O/HCl and the solvent was removed *in vacuo*. The solid product obtained was triturated in Et_2O, yielding 365 mg of the title compound.

PROCEDURE E -Example 1-
(-)-3-[N-(3-pyrrolidinoprop-2-yl)phenylamino]-N-propylbenzamide hydrobromide

To a solution of 130 mg (0.33 mmol) of (+)-N-propyl-10-(3-pyrrolidinoprop-2-yl)phenothiazin-2-carboxamide (EP0346238A1) and 1.1 g (4.62 mmol) of $NiCl_2 \cdot 6H_2O$ in 16 ml of a mixture MeOH:THF:H_2O 1:2:1 respectively, 524 mg (13.86 mmol) of $NaBH_4$ were added at room temperature. After 3h the reaction mixture was poured over a pad of celite, the solvent was removed *in vacuo* and the resulting residue was taken up in H_2O and extracted with Ch_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (AcOEt/MeOH/conc.NH_4OH 95:5:0.5). The resulting solid was dissolved in acetone, the solution was brought to acidic ph with 24% HBr and the solvent was removed *in vacuo*. The resulting solid was triturated with $(i\text{-}Pr)_2O$, yielding 50 mg of the title compound.
$[\alpha]^{25}_D$ = -96 (c=0.1, MeOH)

PROCEDURE F -Example 17-
N,N-Diethyl-4-[[N-(dimethylaminoacetyl)-N-(3-methoxyphenyl)] amino]benzamide citrate

A solution of 1.4 g (3.9 mmol) of N,N-diethyl-4-[[N-chloroacetyl-N-(3-methoxyphenyl)]amino]benzamide in 30 ml of a 33% ethanolic solution of dimethylamine was placed in a medium-pressure apparatus and heated overnight at 80°C. The solvent was removed *in vacuo*, the residue brought to acidic pH with 5% HCl and the aqueous phase extracted with Et_2O, then brought to pH 14 with 15% NaOH and extracted with AcOEt. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude reaction mixture was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 90:7:0.7), yielding 1.7 g of the title compound as a free base. 50 mg of product were dissolved in MeOH, an equimolar amount of anhydrous citric acid was added and the solvent was removed *in vacuo*. The resulting solid was triturated with Et_2O, yielding 30 mg of the title compound.

PROCEDURE G -Example 43-
(±)-N-[[4-[N-(3-Methoxyphenyl)-N-[1-methyl-2-(1-pyrrolidinyl)ethyl]] amino]phenyl]-2-methylpropanamide

To a solution of 0.98 g (3.0 mmol) of (±)-N-(4-aminophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoethanamine in 25 ml of dry CH_2Cl_2, 1 g (7.5 mmol) of K_2CO_3 was added. The reaction mixture was cooled to 0°C and, under a nitrogen atmosphere, 0.8 g (7.5 mmol) of isobutyryl chloride dissolved in 10 ml of dry CH_2Cl_2 were added dropwise. After 15 h. at room temperature, water was added, the phases were separed and the organic phase dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 94.5:5:0.5), yielding 1.0 g of the title compound.

PROCEDURE H
(-)-N,N-Diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide trifluoroacetate -Example 45-
and **(+)-N,N-Diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide trifluoroacetate** -Example 46-

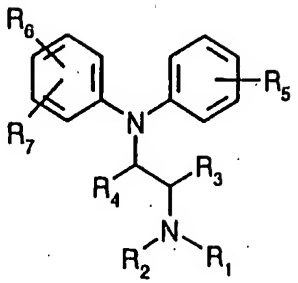
The corresponding racemate was resolved by performing HPLC on chiral stationary phase Chiradex (Merk). Column: Lichrocart 250x21 mm; eluent: KH_2PO_4 (75 mM), TEA (0.2%), pH = 4/ MeCN = 80/20

PROCEDURE I -Example 55-

N,N-Diethyl-4-[[N-(diethylaminoacetyl)-N-(3-hydroxyphenyl)] amino]benzamide Hydrochloride

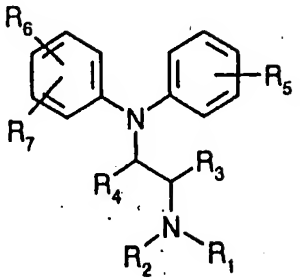
To a solution of 2 g (5.6 mmol) of N,N-diethyl-4-[[N-chloroacetyl-N-(3-methoxyphenyl)]amino]benzamide in 20 ml of toluene, 2.7 ml (25.8 mmol) of diethylamine were added and the resulting solution was heated to 60°C for 15 h. The solvent was removed *in vacuo*, the residue was taken up in water and extracted with CH_2Cl_2, then the organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH/conc.NH_4OH 94.5:5:0.5), yielding 1.9 g of the title compound.

TABLE 4



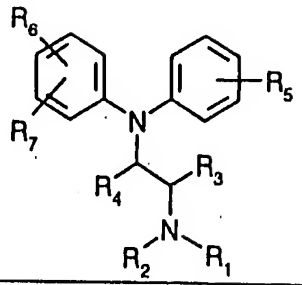
Example	Procedure	Name	R1	R2	R3	R4	R5	R6	R7	optical rot.
1	E	(-)-3-[N-(3-pyrrolidinoprop-2-yl) phenylamino]-N-propylbenzamide HBr	-(CH2)4-		H	Me	H	m-CONH-nPr	H	(-)
2	D	(±)-N-(4-bromophenyl)-N-(3-hydroxyphenyl)-α-methyl-1-pyrrolidinoethanamine HCl	-(CH2)4-		H	Me	OH	p-Br	H	(±)
3	C	(±)-N-(4-bromophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoetanamine citrate	-(CH2)4-		H	Me	OMe	p-Br	H	(±)
4	A	(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(3-pyrrolidinoprop-2-yl)]amino]benzamide citrate	-(CH2)4-		H	Me	OMe	p-CONEt2	H	(±)
5	D	(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(3-pyrrolidinoprop-2-yl)]amino]benzamide citrate	-(CH2)4-		H	Me	OH	p-CONEt2	H	(±)
6	C	N-(4-bromophenyl)-N-(3-hydroxyphenyl)-1-pyrrolidinoethanamine	-(CH2)4-		H	H	OH	p-Br	H	
7	D	N,N-diethyl-4-[[N-(2-dimethylaminoethyl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	H	H	OH	p-CONEt2	H	
8	D	(±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	Me	H	OH	p-CONEt2	H	(±)
9	D	(±)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide oxalate	Me	Me	H	Me	OH	p-CONEt2	H	(±)
10	D	N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinoethyl)]amino] benzamide citrate	-(CH2)4-		H	H	OH	p-CONEt2	H	
11	A	N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinoethyl)]amino] benzamide oxalate	-(CH2)4-		H	H	OMe	p-CONEt2	H	

TABLE 4 -continued-



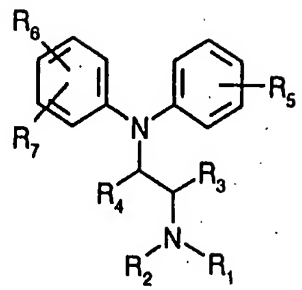
Example	Procedure	Name	R1	R2	R3	R4	R5	R6	R7	optical rot.
12	B	N,N-diethyl-4-[[N-(2-dimethylaminoethyl)-N-(3-methoxyphenyl)]amino]benzamide citrate	Me	Me	H	H	OMe	p-CONEt2	H	
13	D	(±)-N^2-(4-biphenylyl)-N^1,N^1-dimethyl-N^2-(3-hydroxyphenyl)-1,2-propandiamine citrate	Me	Me	H	Me	OH	p-Ph	H	(±)
14	D	(±)-N^1-(4-biphenylyl)-N^2,N^2-dimethyl-N^1-(3-hydroxyphenyl)-1,2-propandiamine citrate	Me	Me	Me	H	OH	p-Ph	H	(±)
15	B	(±)-N^2-(4-biphenylyl)-N^1,N^1-dimethyl-N^2-(3-methoxyphenyl)-1,2-propandiammne citrate	Me	Me	H	Me	OMe	p-Ph	H	(±)
16	B	(±)-N^1-(4-biphenylyl)-N^2,N^2-dimethyl-N^1-(3-methoxyphenyl)-1,2-propandiamine citrate	Me	Me	Me	H	OMe	p-Ph	H	(±)
17	F	N,N-diethyl-4-[[N-(dimethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide citrate	Me	Me	H	C=O	OMe	p-CONEt2	H	(±)
18	B	(±)-1-[4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino] benzoyl]pyrrolidine citrate	Me	Me	H	Me	OMe	p-CON(CH2)4	H	(±)
19	B	(±)-1-[4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino] benzoyl]pyrrolidine citrate	Me	Me	Me	H	OMe	p-CON(CH2)4	H	(±)
20	D	(±)-1-[4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino] benzoyl]pyrrolidine citrate	Me	Me	H	Me	OH	p-CON(CH2)4	H	(±)
21	D	(±)-1-[4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino] benzoyl]pyrrolidina citrate	Me	Me	Me	H	OH	p-CON(CH2)4	H	(±)
22	D	(±)-N,N-diethyl-3-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	H	Me	OH	m-CONEt2	H	(±)

TABLE 4 -continued-



Example	Procedure	Name	R1	R2	R3	R4	R5	R6	R7	optical rot.
23	D	(±)-N,N-diethyl-3-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	Me	H	OH	m-CONEt2	H	(±)
24	D	(±)-N,N-diisopropyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	H	Me	OH	p-CON(i-Pr)2	H	(±)
25	D	(±)-N,N-diisopropyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide citrate	Me	Me	Me	H	OH	p-CON(i-Pr)2	H	(±)
26	D	(±)-N,N-diethyl-3-[[N-(3-hydroxyphenyl)-N-(3-pyrrolidinoprop-2-yl)] amino]benzamide citrate	-(CH2)4-		H	Me	OH	m-CONEt2	H	(±)
27	D	(±)-N,N-diethyl-3-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinoprop-1-yl)] amino]benzamide citrate	-(CH2)4-		Me	H	OH	m-CONEt2	H	(±)
28	D	(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(1-pyrrolidinyl-2-butyl) amino]benzamide HCl	-(CH2)4-		H	Et	OH	p-CONEt2	H	(±)
29	D	(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinyl-1-butyl)]amino]benzamide HCl	-(CH2)4-		Et	H	OH	p-CONEt2	H	(±)
30	B	(±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	Me	H	OMe	p-CONEt2	H	(±)
31	B	(±)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	H	Me	OMe	p-CONEt2	H	(±)
32	B	(±)-N,N-diethyl-3-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	H	Me	OMe	m-CONEt2	H	(±)
33	B	(±)-N,N-diethyl-3-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	Me	H	OMe	m-CONEt2	H	(±)

TABLE 4 -continued-



Example	Procedure	Name	R1	R2	R3	R4	R5	R6	R7	optical rot.
34	B	(±)-N,N-diisopropyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	H	Me	OMe	p-CON(i-Pr)2	H	(±)
35	B	(±)-N,N-diisopropyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	Me	H	OMe	p-CON(i-Pr)2	H	(±)
36	A	(±)-N,N-diethyl-3-[[N-(3-methoxyphenyl)-N-(3-pyrrolidinoprop-2-yl)] amino]benzamide	-(CH2)4-		H	Me	OMe	m-CONEt2	H	(±)
37	A	(±)-N,N-diethyl-3-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinoprop-1-yl)] amino]benzamide	-(CH2)4-		Me	H	OMe	m-CONEt2	H	(±)
38	A	(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(1-pyrrolidinyl-2-butyl)]amino]benzamide HCl	-(CH2)4-		H	Et	OMe	p-CONEt2	H	(±)
39	A	(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinyl-1-butyl)]amino]benzamide HCl	-(CH2)4-		Et	H	OMe	p-CONEt2	H	(±)
40	D	(±)-4-[N-[1-(N-allyl-N-methyl)amino-2-propyl]-N-(3-hydroxyphenyl)amino]-N,N-diethylbenzamide HCl	Me	Allyl	H	Me	OH	p-CONEt2	H	(±)
41	D	(±)-4-[N-[2-(N-allyl-N-methyl)amino-1-propyl] -N-(3-hydroxyphenyl)amino]-N,N-diethylbenzamide HCl	Me	Allyl	Me	H	OH	p-CONEt2	H	(±)
42	D	N,N-diethyl-4-[[N-(dimethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide HCl	Me	Me	H	C=O	OH	p-CONEt2	H	

43	G	(±)-N-[[4-[N-(3-methoxyphenyl)-N-[1-methyl-2-(1-pyrrolidinyl)ethyl]]amino]phenyl]-2-methylpropanamide	-(CH2)4-		H	Me	OMe	p-NHCOi-Pr	H	(±)
44	D	(±)-N-[[4-[N-(3-hydroxyphenyl)-N-[1-methyl-2-(1-pyrrolidinyl)ethyl]]amino]phenyl]-2-methylpropanamide citrate	-(CH2)4-		H	Me	OH	p-NHCOi-Pr	H	(±)
45	H	(-)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide trifluoroacetate	Me	Me	H	Me	OH	p-CONEt2	H	$[a]_D^{20}$= -68.1; c=0.1 MeOH
46	H	(+)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide trifluoroacetate	Me	Me	H	Me	OH	p-CONEt2	H	$[a]_D^{20}$= +60.5; c=0.1 MeOH
47	D	N,N-diethyl-4-[[N-(diethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide HCl	Et	Et	H	C=O	OH	p-CONEt2	H	
48	D	N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(pyrrolidin-1-ylacetyl)]amino]benzamide HCl	-(CH2)4-		H	C=O	OH	p-CONEt2	H	
49	D	N,N-diisopropyl-4-[[N-(dimethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide	Me	Me	H	C=O	OH	p-CON(i-Pr)2	H	
50	D	4-[[N-[[(N-allyl-N-methyl)amino]acetyl]-N-(3-hydroxyphenyl)]amino]-N,N-diethylbenzamide HCl	Me	Allyl	H	C=O	OH	p-CONEt2	H	
51	D	N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(methylaminoacetyl)]amino]benzamide HCl	H	Me	H	C=O	OH	p-CONEt2	H	
52	D	N,N-diisopropyl-4-[[N-aminoacetyl-N-(3-hydroxyphenyl)]amino]benzamide	H	H	H	C=O	OH	p-CON(i-Pr)2	H	
53	A	(±)-4-[N-[1-(N-allyl-N-methyl)amino-2-propyl]-N-(3-methoxyphenyl)amino]-N,N-diethylbenzamide	Me	Allyl	H	Me	OMe	p-CONEt2	H	(±)
54	A	(±)-4-[N-[2-(N-allyl-N-methyl)amino-1-propyl] -N-(3-methoxyphenyl)amino]-N,N-diethylbenzamide	Me	Allyl	Me	H	OMe	p-CONEt2	H	(±)
55	I	N,N-diethyl-4-[[N-(diethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide	Et	Et	H	C=O	OMe	p-CONEt2	H	

56	I	N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(pyrrolidin-1-ylacetyl)]amino]benzamide	-(CH2)4-		H	C=O	OMe	p-CONEt2	H	
57	F	N,N-diisopropyl-4-[[N-(dimethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide	Me	Me	H	C=O	OMe	p-CON(i-Pr)2	H	
58	I	4-[[N-[[(N-allyl-N-methyl)amino]acetyl]-N-(3-methoxyphenyl)]amino]-N,N-diethylbenzamide	Me	Allyl	H	C=O	OMe	p-CONEt2	H	
59	F	N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(methylaminoacetyl)]amino]benzamide	H	Me	H	C=O	OMe	p-CONEt2	H	
60	F	N,N-diisopropyl-4-[[N-aminoacetyl-N-(3-methoxyphenyl)]amino]benzamide	H	H	H	C=O	OMe	p-CON(i-Pr)2	H	
61	C	(±)-N-(4-aminophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoetanamine	-(CH2)4-		H	Me	OMe	p-NH2	H	(±)

TABLE 5

Ex.	NMR	MS	IR cm^{-1} (KBr)
1	(CDCl3): 11.40(s br,1H); 8.00(s br,1H); 7.60(d,1H); 7.37(dd,2H); 7.25(dd,1H); 7.18(dd,1H); 7.08(d,2H); 6.89(d br,1H); 5.25(m,1H); 4.00-3.80(m,2H); 3.60-3.40(m,1H); 3.49(dt,2H); 3.30-3.20(m,1H); 2.30-2.00(m,4H); 1.77(ddq,2H); 1.41(d,3H); 1.00(t,3H).	365 (M+.);281 EI;source 200 C;70 V;200 uA	3420, 2960, 1640.
2	(CDCl3): 10.58(s br,1H); 8.30(s br,1H); 7.36(d,2H); 7.11(dd,1H); 6.85(d,2H); 6.70(s br,1H); 6.63(d,1H); 6.36(d,1H);4.84(ddq,1H); 4.00-3.70(m,2H); 3.36(dd,1H); 3.11(dd,1H); 3.00-2.70(m,2H); 2.30-1.90(m,4H);1.40(d,3H).	374-376 (M+.),290-292,84 EI;source 200 C;70 V;200 uA	2980, 1585, 1490.
3	(DMSO): 11.00(s br,4H); 7.41(d,2H); 7.27(dd,1H); 6.78(d,2H); 6.72(d,1H); 6.52(d,1H); 6.50(s,1H); 4.35(ddq,1H); 3.72(s,3H); 3.40-2.80(m,6H); 2.60(ABq,4H); 1.80(s br,4H); 1.10(d,3H).	388-390 (M+.);304-306;84 EI;source 200 C;70 V;200 uA	3440, 1730, 1580.
4	(DMSO): 10.80(s br,4H); 7.33(dd,1H); 7.23(d,2H); 6.82(d,1H); 6.74(d,2H); 6.63(d,1H); 6.62(s,1H); 4.50(ddq,1H); 3.75(s,3H); 3.30(q br,4H); 3.10-2.70(m,6H); 2.60(ABq,4H); 1.82(s br,4H); 1.15(d,3H); 1.10(t,6H).	409 (M+.);325;84 EI;source 200 C;70 V;200 uA	2960, 1610, 1430 (free base).
5	(DMSO): 10.80(s br,4H); 9.45(s br,1H); 7.22(d,2H); 7.21(dd,1H); 6.73(d,2H); 6.66(dd,1H); 6.52(d,1H); 6.46(dd,1H); 4.47(ddq,1H); 3.32(q br,4H); 3.10-2.80(m,6H); 2.60(ABq,4H); 1.84(s br,4H); 1.16(d,3H); 1.10(t,3H).	395 (M+.);311;211;84 EI;source 200 C;70 V;200 uA	2980, 1730, 1600.
6	(DMSO): 9.30(s,1H); 7.36(d,2H); 7.09(dd,1H); 6.86(d,2H); 6.47(d,1H); 6.45(s,1H); 6.42(d,1H); 3.72(t,2H); 2.60(t,2H); 2.44(m,4H); 1.65(m,4H).	360-362 (M+.);276-278;84 EI;source 200 C;70 V;200 uA	1620, 1570, 1485.
7	(DMSO): 11.00(s br,4H); 9.45(s br,1H); 7.24(d,2H); 7.17(dd,1H); 6.88(d,2H); 6.58(d,1H); 6.54(d,1H); 6.52(s,1H); 3.90(t,2H); 3.32(q br,4H); 2.92(t,2H); 2.59(ABq,4H); 2.55(s,6H); 1.10(t,6H).	355 (M+.);297;197;58 EI;source 200 C;70 V;200 uA	3420, 1730, 1600.
8	(DMSO): 11.00(s br,4H); 9.45(s br,1H); 7.25(d,2H); 7.17(dd,1H); 6.90(d,2H); 6.60(d,1H); 6.55(d,1H); 6.50(s,1H); 3.92(dd,1H); 3.72(dd,1H); 3.40-3.20(m,5H); 2.60(ABq,4H); 1.10(d,3H); 1.09(t,3H).	369 (M+.);298;72 EI;source 200 C;70 V;200 uA	3400, 1730, 1600.
9	(DMSO): 7.20(d,2H); 7.20(dd,1H); 6.70(d,2H); 6.65(d,1H); 6.51(d,1H); 6.44(s,1H); 4.55(ddq,1H); 3.50(dd,1H); 3.40(dd,1H); 3.30(q br,4H); 2.60(s,6H); 1.01(d,3H); 1.06(t,3H).	369 (M+.);311;211;58 EI;source 200 C;70 V;200 uA	3200, 1600, 1450 (free base).
10	(DMSO): 11.00(s br,4H); 9.45(s br,1H); 7.25(d,2H); 7.15(dd,1H); 6.85(d, 2H); 6.60(d,1H); 6.55(d,1H); 6.50(s,1H); 3.95(t,2H); 3.40-3.00(m,10H); 2.60(ABq, 4H); 1.85(m,4H); 1.12(t,6H).	381 (M+.);297;84 EI;source 200 C;70 V;200 uA	2980, 1730, 1600.
11	(DMSO): 7.30(dd,1H); 7.25(d,2H); 6.90(d,2H); 6.71(m,3H); 4.03(t,2H); 3.75(s,3H); 3.40-3.10(m,10H); 1.88(m,4H); 1.10(t,6H).	395 (M+.);311;211;84 EI;source 200 C;70 V;200 uA	2975, 1730, 1620.

TABLE 5 -continued-

Ex.	NMR	MS	IR cm^{-1} (KBr)
12	(DMSO): 11.00(s br,4H); 7.28(dd,1H); 7.24(d,2H); 7.90(d,2H); 6.70(d,1H); 6.70(d,1H); 6.68(s,1H); 3.93(t,2H); 3.74(s,3H); 3.34(d br,4H); 2.91(t,2H); 2.59(ABq,4H); 2.52(s,6H); 1.10(t,6H).	369 (M+.);311;211;58 EI;source 200 C;70 V;200 uA	2980, 1620, 1600 (free base).
13	(DMSO): 11.00(s br,4H); 9.34(s br,1H); 7.62(d,2H); 7.58(d,2H); 7.42(dd,2H); 7.30(dd,1H); 7.14(dd,1H); 6.71(d,2H); 6,52(dd,1H); 6.45(dd,1H); 6.36(dd,1H); 4,47(ddq,1H); 2.80(m,1H); 2.60(ABq,4H); 2.55(s,6H); 2.50(m,1H); 1.12(d,3H).	346 (M+.);288;58 EI;source 200 C;70 V;200 uA	3400, 1720, 1600.
14	(DMSO): 11.00(s br,4H); 9.35(s br,1H); 7.62(d,2H); 7.59(d,2H); 7.43(dd,2H); 7.30(dd,1H); 7.14(dd,1H); 7.07(d,2H); 6.55(dd,1H); 6.49(d,1H); 6.48(d,1H); 4.01(dd,1H); 3.75(dd,1H); 3.33(m,1H); 2.60(s,6H); 2.58(ABq,4H); 1.19(d,3H).	346 (M+.);275;274;72 EI;source 200 C;70 V;200 uA	3400, 1720, 1600.
15	(DMSO): 11.00(s br,4H); 7.66(d,2H); 7.60(d,2H); 7.43(dd,2H); 7.31(dd,1H); 7.25(dd,1H); 6.94(d,2H); 6.67(dd,1H); 6.53(d,1H); 6.51(s, 1H); 4.52(ddq,1H); 3.70(s,3H); 2.78(m,1H); 2.60(ABq,4H); 2.52(m,1H); 2.51(s,6H); 1.15(d, 3H).	360 (M+.);302;58 EI;source 200 C;70 V;200 uA	2985, 1600, 1490 (free base).
16	(DMSO): 11.00(s br,4H); 7.63(d,2H); 7.60(d,2H); 7.43(dd,2H); 7.31(dd,1H); 7.24(dd,1H); 7.09(d,2H); 6.68-6.61(m,3H); 4.02(dd,1H); 3.79(dd,1H); 3.72(s,3H); 3.31(m,1H); 2.59(s,6H); 2.58(ABq,4H); 1.18(d,3H).	360 (M+.); 289;288;72 EI;source 200 C;70 V;200 uA	2985, 1600, 1490 (free base).
17	(DMSO, 353 K): 7.42-7.31(m,5H); 7.00-6.92(m,3H); 3.80(s,3H); 3.40-3.30(m,6H); 2.68(ABq,4H); 2.42(s,6H); 1.10(t,6H).	383 (M+.);355;325;225;58 EI;source 200 C;70 V;200 uA	1730, 1690, 1600.
18	(DMSO): 11.00(s br,4H); 7.40(d,2H); 7.35(dd,1H); 6.86(dd,1H); 6.71-6.63(m,4H); 4.51(m,1H); 3.74(s,3H); 3.43(m,4H); 2.73(m,1H); 2.62(ABq,4H); 2.55(m,1H); 2.50(s,3H); 1.80(m,4H); 1.11(d,3H).	381 (M+.);323;58 EI;source 200 C;70 V;200 uA	2960, 1600, 1400 (free base).
19	(DMSO): 11.00(s br,4H); 7.42(d,2H); 7.31(dd,1H); 6.89(d,2H); 6.76(m,3H); 4.01(dd,1H); 3.81(dd,1H); 3.74(s,3H); 3.43(m,4H); 3.38-3.22(m,1H); 2.61(ABq,4H); 2.60(s,6H); 2.80(m,4H); 1.15(d,3H).	381 (M+.);310;309;72 EI;source 200 C;70 V;200 uA	2960, 1600, 1400 (free base).
20	(DMSO): 10.80(s br,4H); 9.50(s br,1H); 7.39(d,2H); 7.23(dd,1H); 6.69(dd,1H); 6.68(d,2H); 6.55(dd,1H); 6.49(d,1H); 4.50(ddq,1H); 3.40(m,4H); 2.75(m,1H); 2.60(ABq,4H); 2.55(m,1H); 1.83(m,4H); 1.10(d,3H).	367 (M+.);309;58 EI;source 200 C;70 V;200 uA	2960, 1600, 1430 (free base).
21	(CDCl3): 7.33(d,2H); 7.04(dd,1H); 6.81(d,2H); 6.66(dd,1H); 6.54(dd,1H); 6.44(dd,1H); 4.20(dd,1H); 3.65(dd,1H); 3.55-3.35(m,5H); 2.72(ABq,4H); 1.90-1.75(m,4H);1.25(d,3H).	367 (M+.);296;295;72 EI;source 200 C;70 V;200 uA	2960, 1600, 1440 (free base).
22	(DMSO): 10.80(s br,4H); 9.40(s br,1H); 7.30(dd,1H); 7,14(dd,1H); 6.92(dd,1H); 6.85(d,1H); 6.65(s br,1H); 6.55(dd,1H); 6.44(dd,1H); 6.34(dd,1H); 4.46(ddq,1H); 3.40-3.10(m,4H); 2.75(dd,1H); 2.61(ABq,4H); 2.60(dd,1H); 1.10(d,3H); 1.00(m,6H).	369 (M+.);311;58 EI;source 200 C;70 V;200 uA	3420, 1730, 1690.

TABLE 5 -continued-

Ex.	NMR	MS	IR cm^{-1} (KBr)
23	(DMSO); 10.90(s br,4H); 9.40(s br,1H); 7.33(dd,1H); 7.13(dd,1H); 7.06(dd,1H); 6.88(d,1H); 6.81(s,1H); 6.54(dd,1H); 6.50(d,1H); 6.45(s br,1H); 3.99(dd,1H); 3.74(dd,1H); 3.40-3.10(m,5H); 2.61(s,6H); 2.60(ABq,4H); 1.18(d,3H); 1.15-0.90(m,6H).	369 (M+.);298;72 EI;source 200 C;70 V;200 uA	3420, 1730, 1590.
24	(DMSO): 10.85(s br,4H); 9.42(s br,1H); 7.20(dd,1H); 7.14(d,2H); 6.71(d,2H); 6.64(dd,1H); 6.50(dd,1H); 6.44(dd,1H); 4.46(ddq,1H); 3.70(m,2H); 2.73(dd,1H); 2.61(ABq,4H); 2.51(dd,1H); 2.51(s,6H); 1.26(d,12H); 1.13(d,3H).	397 (M+.);339;297;211;58 EI;source 200 C;70 V;200 uA	2960, 1735, 1595.
25	(DMSO): 10.95(s br,4H); 9.45(s br,1H): 7.17(d,2H); 7.16(dd,1H); 6.90(d,2H); 6.60(dd,1H); 6.55(d,1H); 6.53(s br,1H); 3.96(dd,1H); 3.80-3.65(m,3H); 3.35-3.20(m,2H); 2.59(ABq,4H); 2.57(s,6H); 1.27(d,12H); 1.15(d,3H).	397 (M+.);325;197;72 EI;source 200 C;70 V;200 uA	2960, 1735, 1595.
26	(DMSO): 10.90(s br,4H); 9.40(s br,1H); 7.32(dd,1H); 7.16(dd,1H); 6.93(dd,1H); 6.87(d,1H); 6.67(s br,1H); 6.55(dd,1H); 6.44(dd,1H); 6.36(dd,1H); 4.48(ddq,1H); 3.50-2.80(m,10H); 2.60(ABq,4H); 1.85(m,4H); 1.15(d,3H); 1.05(m,6H).	395 (M+.);311;84 EI;source 200 C;70 V;200 UA	2970, 1595, 1450 (free base).
27	(DMSO): 11.00(s br,4H); 9.40(s br,1H); 7.33(dd,1H); 7.14(dd,1H); 7.06(dd,1H); 6.88(d,1H); 6.83(s br,1H); 6.54(d,1H); 6.48(d,1H); 6.46(s br,1H); 4.09(dd,1H); 3.76(dd,1H); 3.50-3.00(m,9H); 2.60(ABq,4H); 1.85(m,4H); 1.22(d,3H); 1.00(m,6H).	395 (M+.);298;297;98 EI;source 200 C;70 V;200 uA	2970, 1595, 1450 (free base).
28	(DMSO): 10.08(s br,1H); 9.55(s br,1H); 7.23(d,2H); 7.22(dd,1H); 6.85(d,2H); 6.66(dd,1H); 6.60(dd,1H); 6.54(dd,1H); 4.55(dddd,1H); 3.70-3.40(m,6H); 3.40-3.25(m,4H); 2.10-1.90(m,4H); 1.75-1.50(m,2H); 1.10(t,6H); 0.99(t,3H).	409(M+.);325;84 EI;source 200 C;70 V;200 uA	3410, 2970, 1600.
29	(DMSO): 10.40 (s br,1H); 9.52(s br,1H); 7.26(d,2H); 7.19(dd,1H); 6.95(d,2H); 6.64(dd,1H); 6.58(dd,1H); 6.56(d,1H); 4.13(dd,1H); 3.99(dd,1H); 3.68-3.56(m, 1H); 3.54-3.41(m,1H); 3.40-3.25(m,5H); 3.25-3.10(m,2H); 2.05-1.70(m,6H); 1.10(t,6H); 0.91(t,3H).	409(M+.);297;197;112 EI;source 180 C;70 V;200 uA	3180, 2970, 1600.
30	(CDCl3): 7.35(m,3H), 6.75-6.55(m,5H); 4.3(m,1H); 3.8(s,3H); 3.4(m,4H); 2.5-2.4(m,1H); 2.35(s,6H); 2.1(m,1H); 1.2(t,9H).	383(M+.);325 EI;source 200 C;70 V;200 uA	2970, 1620, 1595.
31	(CDCl3): 7.30-7.20(m,3H), 6.90(m,2H); 6.70-6.55(m,3H); 3.85(m,1H); 3.8(s,3H); 3.75-3.45(m,5H); 2.95(m,1H); 2.25(s,6H); 1.2(t,6H); 1.0(d,3H).	383(M+.);312 EI;source 200 C;70 V;200 uA	2970, 1620, 1595.
32	-	-	2980, 1635,1595.
33	-	-	2980, 1635,1595.
34	-	-	2990, 1630, 1600.
35	-	-	2990, 1630, 1600.
36	-	-	2960, 1630, 1580.
37	-	-	2960, 1630, 1580.

TABLE 5 -continued-

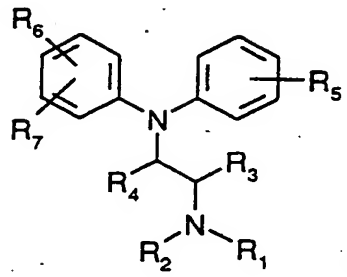
Ex.	NMR	MS	IR cm^{-1} (KBr)
38	(DMSO): 10.2(s br,1H); 7.40-7.20(m,3H); 6.90-6.70(m,5H); 4.55(dddd,1H); 3.85(s,3H); 3.80-3.30(m,9H); 2.10-1.60(m,7H); 1.10(t,6H); 0.95(t,3H).	423(M+.);339;84. EI;source 200 C;70 V;200 uA	2980, 1600, 1490.
39	(DMSO): 10.70 (s br,1H); 7.27(m,3H); 7.05(m,2H); 6.7(m,3H); 4.50-4.00(m,6H); 3.85(s,3H); 3.80-3.30(m, 9H); 2.00-1.70(m,2H); 1.10(t,6H); 0.91(t,3H).	423(M+.);311;211;112. EI;source 200 C;70 V;200 uA	2980, 1600, 1490.
40	(DMSO): 10.20(s br,1H); 9.50(s,1H); 7.24(d,2H); 7.22(dd,1H); 6.80(m,2H); 6.69(d,1H); 6.56(dd,1H); 6.49(d,1H); 6.04-5.86(m,1H); 5.47(m,2H); 4.80-4.68(m,1H); 3.90-3.70(m,2H); 3.31(q br,4H); 3.25-3.01(m,2H); 2.82(s br,3H); 1.23(d,3H); 1.12(t,6H).	395 (M+.);311,211,84 EI; TSQ 700; sorgente 180 C;70 V; 200 uA	3410, 2970, 1600.
41	(DMSO): 10.22 and 10.10(s br,1H); 9.50(s br,1H); 7.25(d,2H); 7.19(dd,1H); 6.99-6.92(m,2H); 6.64(d,1H); 6.58(d,1H); 6.55(s,1H); 5.98-5.82(m,1H); 5.55-5.38(m,2H); 4.20(dd,1H); 4.00-3.77(m,2H); 3.75-3.63(m,1H); 3.60-3.50(m,1H); 3.32(q br,4H); 2.73 and 2.70(d,3H); 1.35 and 1.27(d,3H); 1.10(t,3H).	395 (M+.);298;297,197,98 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3180, 2970, 1600.
42	(DMSO - 353 K): 10.05(s br,1H); 9.72(s br,1H); 7.44(ABq,1H); 7.41(ABq,1H); 7.28(dd,1H); 6.90(d br,1H); 6.87-6.83(m,2H); 4.05(s,2H); 3.35(q,4H); 2.87(s,6H); 1.11(t,3H).	370 (MH+) CI;gas reagente isobutano;P 4000 mTorr;sorgente 150 C;	3400, 1680, 1605.
43	(CDCl3): 7.49(d,2H); 7.11(s br,1H); 7.07(dd,1H); 7.02(d,2H); 6.36(d,1H); 6.29(d,1H); 6.28(s,1H); 4.30-4.20(m,1H); 3.72(s,3H); 2.61-2.46(m,6H); 2.35(dd,1H); 1.75(m,4H); 1.23(d,6H); 1.19(d,3H).	395 (M+.);312;311;84 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3280, 2960, 1660.
44	(DMSO): 9.85(s,1H); 9.05(s br,1H); 7.64(d,2H); 7.00(d,2H); 6.95(dd,1H); 6.18(m,2H); 6.02(dd,1H); 4.38(dt,1H); 3.15-2.80(m,6H); 2.62(ABq,1H); 2.59(m,1H); 2.54(ABq,1H); 1.86(m,4H); 1.12(d,3H); 1.11(d,6H).	381(M+); 297; 84 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3300, 2960, 1670.
45	(CDCl3 +TFA): 9.10(s br, 1H); 7.30(dd, 1H); 7.26(dd, 2H); 6.90(d, 1H); 6.80(d, 2H); 6.78(s,1H); 6.62(d,1H); 4.68(m, 1H); 3.71-3.45(m br, 4H); 3.33(m, 1H); 3.10(m, 1H); 3.00(d, 6H); 1.32(m, 9H).	369 (M+); 311 EI; TSQ 700; sorgente 180 C;70 V;200 uA	
46	(CDCl3 +TFA): 9.10(s br,-1H); 7.30(dd, 1H); 7.26(dd, 2H); 6.90(d, 1H); 6.80(d, 2H); 6.78(s,1H); 6.62(d,1H); 4.68(m, 1H); 3.71-3.45(m br, 4H); 3.33(m, 1H); 3.10(m, 1H); 3.00(d, 6H); 1.32(m, 9H).	369 (M+); 311 EI; TSQ 700; sorgente 180 C;70 V;200 uA	
47	(DMSO): 10.05(s br,1H): 9.51(s br,1H); 7.70-7.13(m,5H); 7.05-6.70(m,3H); 3.95(s,2H); 3.49-3.14(m, 8H); 1.20(t, 6H); 1.10(s br, 6H).	398 (MH+); 86 CI;gas reagente isobutano;P 4000 mTorr;sorgente 150 C;	3400, 1680, 1600.
48	(DMSO): 10.19(s br,1H); 10.01(s br,1H); 7.60-7.20(m,5H); 7.00-6.70(m,3H); 4.11(s,1H); 3.60-3.00(m, 8H); 1.90(m,4H); 1.10(m,6H).	396 (MH+); 84 CI;gas reagente isobutano;P 4000 mTorr;sorgente 150 C;	3450, 1675, 1605.
49	(CDCl3): 7.27(s,4H); 7.15(dd,1H); 6.73(m,2H); 6.66(d,1H); 3.75(m br,2H); 3.10(s,3H); 2.32(s,6H); 1.35(m br,12H);	397 (M+); 369; 58 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3400, 1680, 1600.

TABLE 5 -continued-

50	(CDCl3 - as a base): 7.36(d,2H); 7.28(d,2H); 7.20(dd,1H); 6.77(d,1H); 6.72(m,2H); 5.86-5.73(m,1H); 5.21-5.12(m,2H); 3.61-3.45(m br,2H); 3.45-3.26(m br,2H); 3.20(s,2H); 3.15(d,2H); 2.37(s,3H); 1.20(m br,6H).	395 (M+); 325; 84; 41 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3400, 1675, 1600.
51	(CDCl3): 7.40(m,4H); 7.30(dd,1H); 6.84(d,1H); 6.73(d,1H); 6.72(s,1H); 3.70-3.10(m,6H); 3.40(s,2H); 2.51(s, 3H); 1.30(s br,6H).	355 (M+); 284;212 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3450, 1680, 1610.
52	(CDCl3 + TFA): 7.48(s br, 5H); 7.35(m, 5H); 7.00(d,1H); 6.88(d, 1H); 6.80(s, 1H); 3.91(s br, 2H); 3.75(m,2H); 1.55(d, 3H); 1.22(d,3H).	369(M+); 312;269;212 EI; TSQ 700; sorgente 180 C;70 V;200 uA	3400, 1675, 1600.
53	-	-	2990, 1630, 1600.
54	-	-	2980, 1630, 1590.
55	-	-	2990, 1680, 1590.
56	-	-	2990, 1675, 1600.
57	-	-	2980, 1675, 1600.
58	-	-	2990, 1680, 1600.
59	-	-	2990, 1675, 1595.
60	-	-	3000, 1680, 1600.
61	-	-	3370. 2960, 1610

Claims

1. A compound, or solvate or salt thereof, of formula (I)



(I)

in which,

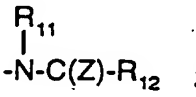
R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by an oxygen;

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, thiol or alkylthio;

R_6 is phenyl, halogen, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur;

R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl,

or R_6 is a para or meta  group

in which R_{11} and R_{12} which may be the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl, or halogen.

2. A compound according to claim 1 in which each of R_1 and R_2 is methyl, ethyl, cyclopropylmethyl, allyl, or together with the N atom, pyrrolidino.

3. A compound according to claim 1 or 2, in which each of R_3 and R_4 is hydrogen, methyl, ethyl, iso-propyl or oxo.

4. A compound according to any one of claims 1 to 3 in which R_5 is hydrogen, hydroxy or methoxy.

5. A compound according to any one of claims 1 to 4 in which R_6 is COMe, CO-i-Pr, COOEt, $CONH_2$, CONH-n-Pr, CON(Me)Et, CON(Me)i-Pr, $CONEt_2$, $CON(i\text{-}Pr)_2$, CONEt(i-Pr), $CON(\text{-}CH_2\text{-})_4$, NHCOi-Pr, NH_2, bromine or phenyl.

6. A compound according to any one of claims 1 to 5 in which R_7 is hydrogen or methyl.

7. A compound selected from:

(-)-3-[N-(3-pyrrolidinoprop-2-yl) phenylamino]-N-propylbenzamide;

(±)-N-(4-bromophenyl)-N-(3-hydroxyphenyl)-α-methyl-1-pyrrolidinoethanamine;

(±)-N-(4-bromophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoetanamine;

(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(3-pyrrolidinoprop-2-yl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(3-pyrrolidinoprop-2-yl)]amino]benzamide;

N-(4-bromophenyl)-N-(3-hydroxyphenyl)-1-pyrrolidinoethanamine;

N,N-diethyl-4-[[N-(2-dimethylaminoethyl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinoethyl)]amino] benzamide;

N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinoethyl)]amino] benzamide;

N,N-diethyl-4-[[N-(2-dimethylaminoethyl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N^2-(4-biphenylyl)-N^1,N^1-dimethyl-N^2-(3-hydroxyphenyl)-1,2-propandiamine;

(±)-N^1-(4-biphenylyl)-N^2,N^2-dimethyl-N^1-(3-hydroxyphenyl)-1,2-propandiamine;

(±)-N^2-(4-biphenylyl)-N^1,N^1-dimethyl-N^2-(3-methoxyphenyl)-1,2-propandiammne;

(±)-N^1-(4-biphenylyl)-N^2,N^2-dimethyl-N^1-(3-methoxyphenyl)-1,2-propandiamine;

N,N-diethyl-4-[[N-(dimethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-1-[4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino] benzoyl]pyrrolidine;

(±)-1-[4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino] benzoyl]pyrrolidine;

(±)-1-[4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino] benzoyl]pyrrolidine;

(±)-1-[4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino] benzoyl]pyrrolidina;

(±)-N,N-diethyl-3-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-3-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diisopropyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diisopropyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-3-[[N-(3-hydroxyphenyl)-N-(3-pyrrolidinoprop-2-yl)] amino]benzamide;

(±)-N,N-diethyl-3-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinoprop-1-yl)] amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(1-pyrrolidinyl-2-butyl) amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(2-pyrrolidinyl-1-butyl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-3-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-3-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diisopropyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diisopropyl-4-[[N-(2-dimethylaminoprop-1-yl)-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N,N-diethyl-3-[[N-(3-methoxyphenyl)-N-(3-pyrrolidinoprop-2-yl)] amino]benzamide;

(±)-N,N-diethyl-3-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinoprop-1-yl)] amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(1-pyrrolidinyl-2-butyl)]amino]benzamide;

(±)-N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(2-pyrrolidinyl-1-butyl)]amino]benzamide;

(±)-4-[N-[1-(N-allyl-N-methyl)amino-2-propyl]-N-(3-hydroxyphenyl)amino]-N,N-diethylbenzamide;

(±)-4-[N-[2-(N-allyl-N-methyl)amino-1-propyl] -N-(3-hydroxyphenyl)amino]-N,N-diethylbenzamide;

N,N-diethyl-4-[[N-(dimethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-N-[[4-[N-(3-methoxyphenyl)-N-[1-methyl-2-(1-pyrrolidinyl)ethyl]]amino]phenyl]-2-methylpropanamide;

(±)-N-[[4-[N-(3-hydroxyphenyl)-N-[1-methyl-2-(1-pyrrolidinyl)ethyl]]amino]phenyl]-2-methylpropanamide;

(-)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-;hydroxyphenyl)]amino]benzamide;

(+)-N,N-diethyl-4-[[N-(3-dimethylaminoprop-2-yl)-N-(3-hydroxyphenyl)]amino]benzamide;

N,N-diethyl-4-[[N-(diethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide;

N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(pyrrolidin-1-ylacetyl)]amino]benzamide;

N,N-diisopropyl-4-[[N-(dimethylaminoacetyl)-N-(3-hydroxyphenyl)]amino]benzamide;

4-[[N-[[(N-allyl-N-methyl)amino]acetyl]-N-(3-hydroxyphenyl)]amino]-N,N-diethylbenzamide;

N,N-diethyl-4-[[N-(3-hydroxyphenyl)-N-(methylaminoacetyl)]amino]benzamide;

N,N-diisopropyl-4-[[N-aminoacetyl-N-(3-hydroxyphenyl)]amino]benzamide;

(±)-4-[N-[1-(N-allyl-N-methyl)amino-2-propyl]-N-(3-methoxyphenyl)amino]-N,N-diethylbenzamide;

(±)-4-[N-[2-(N-allyl-N-methyl)amino-1-propyl] -N-(3-methoxyphenyl)amino]-N,N-diethylbenzamide;

N,N-diethyl-4-[[N-(diethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide;

N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(pyrrolidin-1-ylacetyl)]amino]benzamide;

N,N-diisopropyl-4-[[N-(dimethylaminoacetyl)-N-(3-methoxyphenyl)]amino]benzamide;

4-[[N-[[(N-allyl-N-methyl)amino]acetyl]-N-(3-methoxyphenyl)]amino]-N,N-diethylbenzamide;

N,N-diethyl-4-[[N-(3-methoxyphenyl)-N-(methylaminoacetyl)]amino]benzamide;

N,N-diisopropyl-4-[[N-aminoacetyl-N-(3-methoxyphenyl)]amino]benzamide;

(±)-N-(4-aminophenyl)-N-(3-methoxyphenyl)-α-methyl-1-pyrrolidinoetanamine

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

9. A compound according to any one of claims 1 to 7 for use as an active therapeutic substance.

10. A compound according to any one of claims 1 to 7 for use as an analgesic, immunosuppressant to prevent to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agent, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough and respiratory depression, mental illness, epileptic seizures and other neurologic disorders.

11. The use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for use as an analgesic, immunosuppressant to prevent rejection in organ transplant and skin graft, anti-allergic and anti-inflammatory agent, brain cell protectant, for the treatment of drug and alcohol abuse, to decrease gastric secretion, for the treatment of diarrhoea, cardiovascular and respiratory diseases, cough and respiratory depression, mental illness, epileptic seizures and other neurologic disorders.

12. A method for the treatment and/or prophylaxis in mammals, particularly humans, of the therapeutic conditions as defined in claim 11, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 7.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 96/02152

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/12 C07C237/30 C07C237/42 C07C215/82 C07C217/92
A61K31/165 A61K31/135 A61K31/395 C07D295/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,970 646 (DR. A. WANDER S.A.) 1962 cited in the application see page 2, line 50 - line 51 see page 3, line 28 - line 29 ---	1-4
X	EP,A,0 397 556 (RHONE POULENC SANTE) 14 November 1990 see page 14, line 11 --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
10 September 1996	20.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Pauwels, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 96/02152

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 2, 1946, LETCHWORTH GB, pages 5-10, XP002012977 F.E. KING ET AL.: "New potential chemotherapeutic agents. Part III. Derivatives of diphenylamine and of alpha,alpha-diphenylmethylamine" see page 7, last paragraph - page 8, paragraph 1 ---	1-4
A	WO,A,93 15062 (WELLCOME FOUND) 5 August 1993 cited in the application see claims -----	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 96/02152

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/02152

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-970646		FR-A-	1278405	30-10-61
		US-E-	RE25788	
		US-A-	3042045	03-07-62
EP-A-0397556	14-11-90	FR-A-	2646847	16-11-90
		CA-A-	2016439	12-11-90
		DE-D-	69003998	25-11-93
		DE-T-	69003998	03-03-94
		ES-T-	2060097	16-11-94
		JP-A-	3056453	12-03-91
		US-A-	5223529	29-06-93
WO-A-9315062	05-08-93	AU-A-	3457393	01-09-93
		EP-A-	0649414	26-04-95
		JP-T-	7503247	06-04-95
		NZ-A-	246916	27-08-96
		ZA-A-	9300717	02-08-94